REMARKS

Applicants request reexamination and reconsideration of the present application, as amended, pursuant to and consistent with 37 C.F.R. §112, in light of the remarks which follow.

Claims 21-25, 27-34 and 45-47 are now in this application. Claims 19-20, 26 and 35-44 have been cancelled and Claims 45-47 have been added by the foregoing amendment. Claims 1-18 were previously cancelled.

With respect to the new claims, all of Claims 45-47 read on the elected invention. Claim 45 replaces original Claim 19 as the broadest claim in the application. Claims 46 and 47 are dependent claims drawn to a preferred embodiment of the invention disclosed on page 6, lines 14-19 of the specification. No new matter has been added.

In response to the restriction requirement, applicants hereby affirm the election, without traverse, of Group I. Claims 21-25, 27-34 and new Claims 45-47 read on the elected Group I. As the election was made without traverse, applicants have cancelled the claims drawn to the non-elected subject matter, namely Claims 1-18, 20, 26 and 35-44. Thus, applicants have fully complied with the restriction requirement.

Claims 21-25, 27-34 and 45-47 are now presented for examination on the merits.

Claims 19, 21-25 and 27-34 have been rejected under 35 U.S.C. §101 and under 35 U.S.C. §112, first paragraph, because they are drawn to a regime/regimen. Without conceding the merits of these rejections, applicants have substituted "method" in place of regime/regimen, in the claims, as suggested by the Examiner. These rejections thus cannot be maintained against any of the claims now in the application.

Claims 19 and 27-34 have also been rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for "combating signs of cutaneous aging and of hair follicles, to improve the radiance of the skin, to smooth the skin of the face, to treat or prevent wrinkles and fine lines in the skin or to stimulate the epidermal renewal process", does not reasonably provide enablement for methods of treating any and all adverse conditions of the skin, mucosa, nails or keratinous fibers. It is pointed out that Claim 19 (and therefore its dependent claims) was not drawn to methods of treating any and all adverse conditions of the skin, mucosa, nails or keratinous fibers, but only of an adverse or objectionable condition, quite a number of which the Examiner has indicated to be enabled. Nevertheless, in an effort to advance prosecution and without conceding the merits of this rejection, applicants have replaced Claim 19 with new Claim 45, in which each of the methods which the Examiner has indicated to be enabled by the specification is recited. Thus, Claim 45 is believed to fully overcome this enablement rejection. Applicants note that the dependent claims now depend from Claim 45 and thus are also free of this rejection.

Claims 19, 21-25 and 27-34 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite because of the use of certain terms in the claims. Each of these terms is discussed below.

The term "desired", used in the expression "to elicit the desired response", has been replaced with more specific language in each of the independent claims. While it is believed that the nature of the desired response would have been readily understood by one of ordinary skill in the art, the responses are now expressed by the more explicit terms, "to

lessen signs of cutaneous aging or aging of the hair follicles", "to increase the radiance of the skin", "to elicit a smoothing effect on the facial skin", "to lessen the appearance of wrinkles or fine lines in the skin", and "to stimulate epidermal renewal in the skin". There is, moreover, nothing inherently indefinite in using relative terms, as it would be readily understood by the skilled artisan or, indeed, by the person carrying out the method, that the method is accomplished when the signs of aging of the skin or hair are reduced, when the skin looks more radiant than before, when the facial skin is smoother than before, when the appearance of wrinkles or fine lines is reduced or when epidermal renewal has been stimulated.

The expression "such period of time as required" has been replaced with the phrase "for a period of time sufficient to", which is used in conjunction with the more explicit language discussed in the preceding paragraph. It is perfectly clear from this that the period of time is long enough to accomplish the specific results spelled out in the claim.

The expressions "improving" and "preventing" have been removed from the claims, although applicants dispute the merits of the 35 U.S.C. §112, second paragraph, rejection based thereon.

To "smooth" means to make something even or level; this is the normal meaning of the word. Smoothing the skin is simply making the skin more even or level, while eliciting a smoothing effect on the facial skin is simply making the facial skin smoother than prior to treatment. This meaning is clear on its face to the skilled person or indeed to the ultimate user, so it cannot properly be considered to be indefinite.

With respect to the use of the expression "admixture" in Claim 32, the specification clearly teaches that a mixture of glucosylated hydroxystilbenes can be used; see, for example, the final paragraph of page 4 of the description. Applicants have reworded the claim to clarify this point, but would be happy to consider any alternative language the Examiner might suggest.

As to Claims 32-34, applicants have reworded these claims to make them clearer. It is not the precise chemical make-up of the extracts that is required; however, it is essential in these claims that at least one glucosylated hydroxystilbene be extracted from the plants. The specification describes extraction on pages 5 and 6 and also refers to a number of publications which describe extraction procedures. The art of record herein also describes how extracts are prepared; this is known in the art. The claims are believed to be clear in this respect as now presented.

In view of the foregoing, it is believed that the claims now in the application are free of the record 35 U.S.C. §112, second paragraph rejection.

Claims 19, 21-25 and 27-34 have been rejected under 35 U.S.C. §103(a) as unpatentable over Carson et al WO 99/04747 and the Waterhouse et al literature article. Applicants submit that all of the claims now in the application are free of this rejection.

Carson et al teach that resveratrol, a phytoestrogen, is useful in methods of inhibiting the proliferation of keratinocytes and stimulating their differentiation, improving the appearance of wrinkled, lined, dry, flaky, aged or photodamaged skin, improving skin thickness, elasticity, flexibility, radiance, glow and plumpness, according to the abstract and Claims 3 and 4. These methods require an amount of from 0.00002 to 10 wt.% of

resveratrol, according to Carson et al. Carson et al also teach that resveratrol is found in a variety of common edible plants, including red grapes. Page 4, line 1 to page 5, line 9 discuss the art known to Carson et al. The only disclosure noted by Carson et al that mentions any amount of grape to be used for cosmetic purposes is JP 06336421, which teaches the presence of 0.5% of grape extract in its compositions. Carson et al calculate that this would have a resveratrol concentration of 0.33 micromolar or 0.0000075 wt.%, far below the amount deemed effective by Carson et al.

Although Carson et al teach that resveratrol can be found in wine and grapes, they do not teach that wine or grape extracts can be applied to the skin to carry out their claimed methods. They teach only that the compound resveratrol itself can be used in their methods. Most importantly, they do not teach that an effective amount of any derivative of resveratrol, much less a glucosylated resveratrol, could be used topically to improve the skin conditions according to their invention. Indeed, the Carson et al reference is silent as to the possibility of using glucosylated resveratrol or any other glucosylated hydroxystilbene in their method.

Waterhouse et al teach that extracts of grape skin gave a variety of results when the authors analyzed for the presence of resveratrol and piceid, which is 3,4',5-trihydroxystilbene-3-β-mono-D-glucoside. In five different samples from grapes, the following results were obtained: (a) one sample of "Pinot noir" gave the highest level of piceid and no detectable amount of resveratrol; (b) one sample of "Concord" gave no detectable piceid but a detectable amount of resveratrol; (c) one sample of "Syrah" gave 4-5 times as much resveratrol as piceid; (d) one sample of "Pinot noir" gave more than 6 times

as much resveratrol as piceid; and (e) one sample of "Pinot noir" gave 15-20% more resveratrol than piceid. As the authors note, they found no proportionality between the levels of resveratrol and those of piceid. Moreover, they admit that they emphasized recovery of piceid over recovery of resveratrol, and further admit that their data are not precise. At any rate, it is apparent from Waterhouse et al that both piceid and resveratrol can be found in at least some grape/berry skins, while some samples produce no measurable resveratrol and others produce no measurable piceid. The authors suggest on page 572 that the levels of piceid in wine "should be studied to determine whether or not piceid could significantly contribute to the physiologically available pool to humans of resveratrol in wine." This is a suggestion to test wine to see if piceid contributes to the beneficial effects of drinking wine which are noted at the beginning of the Waterhouse et al reference. This is a "whether or not"/"if" situation; it is an invitation to investigate or experiment and does not give the ordinary skilled worked a reasonable expectation of success. Furthermore, it does not suggest topical application of wine for any purpose whatsoever, only oral ingestion.

Indeed, the suggestion by Waterhouse et al that an investigation be conducted into the role of piceid in affecting "the physiologically available amounts of resveratrol to consumers of wine" is made in the context of diseases and biological effects disclosed by those authors. One of the activities noted by Waterhouse et al is the *in vitro* effect in inhibiting the copper-catalyzed oxidation of low density lipoprotein (LDL), a serum cholesterol fraction. This anti-oxidant effect has been subsequently investigated by Teguo and co-workers for glucosylated and unglucosylated hydroxystilbenes, and their results are

reported in Teguo et al, *J. Nat. Prod.* 61, 655-657 (1998). A copy of that publication was earlier made of record by applicants herein together with applicants' August 15, 2001 Information Disclosure Statement.

The Teguo et al publication referred to in the preceding paragraph reports that the glucosylated hydroxystilbenes tested (one of which was piceid) have anti-oxidant activities far inferior to the non-glucosylated hydroxystilbenes tested (one of which was resveratrol). Indeed, the reduction was seven times in the case of (E)-piceid (Compound 3) versus (E)-resveratrol. This is a teaching away from use of glucosylated resveratrol in place of non-glucosylated resveratrol for the biological effects noted by Waterhouse et al. Moreover, as noted above, the Waterhouse et al reference is silent as to topical application for any purpose whatsoever. Certainly, one of ordinary skill would not be motivated toward substituting glucosylated resveratrol for the resveratrol in Carson et al based on the art as a whole, which includes not only Carson et al and Waterhouse et al but also Teguo et al. In fact, in light of Teguo et al, applicants' finding that glucosylated hydroxystilbenes can be used to good effect in methods for improving skin conditions as claimed herein is quite surprising.

It is abundantly clear that applicants' method is not disclosed or suggested by the cited art, taken separately or in combination. Certainly, the prior art references suggest no advantage to combining and modifying them to arrive at applicants' invention. The prior art itself must suggest the reason to combine them (*In re Sernaker*, 217 U.S.P.Q. 1) and indeed it does not. There simply is no basis for combining the cited references, for there is not even an allusion in either one of them for such combination. *United Merchants, etc. v.*

Ladd, 139 U.S.P.Q. 199. Further, where references are combined, it should be considered whether those references suggest doing what applicants did. *In re Gruskin*, 110 U.S.P.Q. 288. The references relied upon here in no way meet that burden. Indeed, the references are silent as to a possible combination and, as was succinctly stated in *In re Burt & Walter*, 148 U.S.P.Q. 548, "Silence in a reference is hardly a proper substitute for an adequate disclosure of facts upon which a conclusion of obviousness may justifiably follow." Also in point as regards the references separately or in combination is *In re Wesslau*, 147 U.S.P.Q. 391, in which the Court stated:

> It is impermissible within the framework of Section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such a reference fairly suggests to one of ordinary skill in the art.

In fact, it is only with the benefit of hindsight that one could arrive at applicants' invention and, as the CAFC succinctly put it in *Orthopedic Equipment Co., Inc. v. United States*, 217 U.S.P.Q 193:

> It is wrong to use the patent in suit as a guide through the maze of prior art references, combining the right references in the right way so as to achieve the result of the claims in suit. Monday morning quarterbacking is quite improper when resolving the question of non-obviousness in a court of law.

When fairly viewed, there is no question but that the cited references simply fail to teach or suggest applicants' invention.

It is clear that the references, separately or in combination, do not suggest using glucosylated hydroxystilbenes in the methods claimed herein. In the case of resveratrol and glucosylated resveratrol, Waterhouse et al show that grape extracts can contain both of

these derivatives. Waterhouse et al. also show, however, that grape extracts vary greatly in their content and that extracts can be obtained which contain no measurable non-glucosylated hydroxystilbenes while other extracts can be obtained which contain no measurable glucosylated hydroxystilbenes. Thus, applicants' method can be readily carried out without using the Carson et al. method which requires resveratrol, even when applicants' glucosylated hydroxystilbenes are derived from wine. It is not applicants' intention to apply the non-glucosylated form in their invention; rather, it is applicants' intention, as discussed in the specification, to use glucosylated hydroxystilbenes, which applicants have found can be converted in the skin or hair follicles to the non-glucosylated hydroxystilbenes and which thus avoid the disadvantages of applying the non-glucosylated hydroxystilbenes themselves directly (also detailed in the specification). The fact that the glucosylated form is converted into the non-glucosylated form in the skin or hair is the discovery of the present inventors which makes the instantly claimed method possible and avoids the disadvantage of direct application of the non-glucosylated compounds.

In view of the foregoing, it is believed that all of the claims as amended above are patentable. Issuance of a Notice of Allowance is believed to be next in order and is earnestly solicited.

Respectfully submitted,

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Marked-up Claims 21-25 and 27-34

21. (Amended) A [regime/regimen] method for combating signs of cutaneous aging [and] or aging of the hair follicles of an individual subject in need of such treatment, comprising topically applying thereon, for [such] a period of time [as required to elicit the desired response] sufficient to lessen the signs of cutaneous aging or aging of the hair follicles, [a thus] an effective amount of at least one glucosylated hydroxystilbene compound[,] or a composition [comprised thereof] comprising an effective amount of at least one glucosylated hydroxystilbene and a physiologically acceptable medium therefor.

22. (Amended) A [regime/regimen] method for [improving] increasing the radiance of the skin of an individual subject in need of such treatment, comprising topically applying thereon, for [such] a period of time [as required to elicit the desired response] sufficient to increase the radiance of the skin, [a thus] an effective amount of at least one glucosylated hydroxystilbene compound[,] or a composition [comprised thereof] comprising an effective amount of at least one glucosylated hydroxystilbene and a physiologically acceptable medium therefor.

23. (Amended) A [regime/regimen] method for smoothing the facial skin of an individual subject in need of such treatment, comprising topically applying thereon, for [such] a period of time [as required to elicit the desired response] sufficient to elicit a smoothing effect on the facial skin, [a thus] an effective amount of at least one glucosylated hydroxystilbene compound[,] or a composition [comprised thereof] comprising an effective

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amount of at least one glucosylated hydroxystilbene and a physiologically acceptable medium therefor.

24. (Amended) A [regime/regimen] method for treating [or preventing] wrinkles [and fines] or fine lines in the skin of an individual subject in need of such treatment, comprising topically applying thereon, for [such] a period of time [as required to elicit the desired response] sufficient to lessen the appearance of wrinkles or fine lines in the skin, [a thus] an effective amount of at least one glucosylated hydroxystilbene compound[,] or a composition [comprised thereof] comprising an effective amount of at least one glucosylated hydroxystilbene and a physiologically acceptable medium therefor.

25. (Amended) A [regime/regimen] method for stimulating epidermal renewal in the skin of an individual subject in need of such treatment, comprising topically applying thereon, for [such] a period of time [as required to elicit the desired response] sufficient to stimulate epidermal renewal in the skin, [a thus] an effective amount of at least one glucosylated hydroxystilbene compound[,] or a composition [comprised thereof] comprising an effective amount of at least one glucosylated hydroxystilbene and a physiologically acceptable medium therefor.

27. (Amended) The [regime/regimen] method as defined by [Claim 19] Claim 45, said at least one glucosylated hydroxystilbene compound having the structural formula (I):

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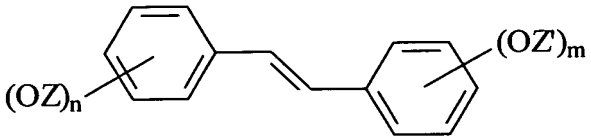
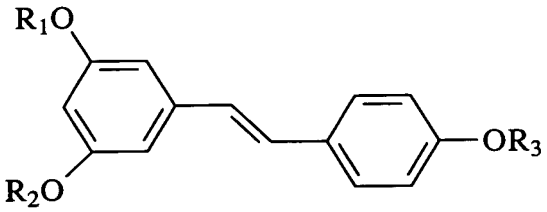
Marked-up Claims 21-25 and 27-34



(I)

wherein n is a whole number ranging from 1 to 5; m is a whole number ranging from 0 to 5; and Z and Z′, which may be identical or different, are each a hydrogen atom or a glucosyl radical, with the proviso that at least one of Z and Z′ is a glucosyl radical.

28. (Amended) The [regime/regimen] method as defined by [Claim 19] Claim 45, said at least one glucosylated hydroxystilbene compound having the structural formula (II):



(II)

wherein the radicals R_1, R_2 and R_3, which may be identical or different, are each a [hydroxyl group,] hydrogen atom or a glucosyl radical, with the proviso that at least one of R_1, R_2 and R_3[,] is a glucosyl radical.

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29. (Amended) The [regime/regimen] method as defined by [Claim 19] Claim 45, said at least one glucosylated hydroxystilbene compound comprising 3,4'-dihydroxystilbene-5-O-beta-glucoside; [3,5-dihydroxystilbene-4'-0-beta-glucoside]3,5-dihydroxystilbene-4'-O-beta-glucoside; 4',5-dihydroxystilbene-3-O-beta-glucoside; 4'-hydroxystilbene-3,5-O-beta-diglucoside; 5-hydroxystilbene-3,4'-O-beta-diglucoside; 3-hydroxystilbene-4',5-O-beta-diglucoside; stilbene-3,4',5-O-beta-triglucoside; 4'-methoxy-3',5-stilbenediol-3-O-beta-glucoside; 3,5,4'-trihydroxystilbene-2-O-beta-glucoside; 3',4,5'-trihydroxystilbene-3-O-beta-glucoside; pinosylvin glucoside; 5-hydroxystilbene-3-O-beta-glucoside; 3-hydroxystilbene-5-O-beta-glucoside; and/or stilbene-3,5-O-beta-diglucoside.

30. (Amended) The [regime/regimen] method as defined by [Claim 19] Claim 45, said at least one glucosylated hydroxystilbene compound comprising the D optical isomer thereof.

31. (Amended) The [regime/regimen] method as defined by [Claim 19] Claim 45, said at least one glucosylated hydroxystilbene compound comprising an admixture [thereof] of glucosylated hydroxystilbene compounds.

32. (Amended) The [regime/regimen] method as defined by [Claim 19] Claim 45, wherein said at least one glucosylated hydroxystilbene compound [comprising a plant extract] is extracted from plants.

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Marked-up Claims 21-25 and 27-34

33. (Amended) The [regime/regimen] method as defined by [Claim 19] Claim 45, wherein said at least one glucosylated hydroxystilbene compound [comprising an extract from] is extracted from *vitis vinifera* or *polygonum cuspidatum* tissue.

34. (Amended) The [regime/regimen] method as defined by [Claim 19,] Claim 45, wherein said at least one glucosylated hydroxystilbene compound [comprising a wine extract] is extracted from wine.